General

Guideline Title

Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays).

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 53 p. (Diagnostics guidance; no. 15).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Institute for Health and Care Excellence (NICE): This guidance considers high-sensitivity troponin tests to be those that have a coefficient of variation of 10% or less at the 99th percentile (the upper limit of the reference population), and are able to detect cardiac troponin in at least 50% of the reference population. These recommendations refer to the use of these tests with early rule-out protocols. NICE is aware that there is a wide range of non-high-sensitivity troponin tests available to the National Health Service (NHS) which are used to rule-out non-ST-segment-elevation myocardial infarction (NSTEMI). The evidence for these tests has not been assessed in this guidance, and the recommendations, therefore, do not relate to the use of non-high-sensitivity troponin tests.

The Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay are recommended as options for the early rule out of NSTEMI in people presenting to an emergency department with chest pain and suspected acute coronary syndrome.

The assays are recommended for use with 'early rule-out protocols', which typically include a blood sample for cardiac troponin I or T taken at initial assessment in an emergency department and a second blood sample taken after 3 hours. Laboratories should report absolute values and the upper reference limit should be set at the 99th percentile. Results should be interpreted along with clinical judgement and the results of clinical assessment. Healthcare professionals should take into account the pre-test probability of NSTEMI, the length of time since the suspected acute coronary syndrome, the possibility of chronically elevated troponin levels in some patients and that 99th percentile thresholds for troponin I and T may differ between sexes. When NSTEMI is not ruled out using an 'early rule-out protocol', further clinical assessment is required to determine whether a diagnosis of NSTEMI is appropriate.

The AccuTnI+3 assay is only recommended for use in clinical research, for early rule out of NSTEMI in people presenting to an emergency

department with chest pain and suspected acute coronary syndrome.

Healthcare professionals using 'early rule-out protocols' including the Elecsys Troponin T high-sensitive or the ARCHITECT STAT High Sensitive Troponin-I assays should collect further information on the time taken to rule out NSTEMI in clinical practice and on the clinical outcomes of people presenting to an emergency department with chest pain and suspected acute coronary syndrome.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Acute chest pain
- Non-ST-segment elevation myocardial infarction (NSTEMI)

Guideline Category

Diagnosis

Evaluation

Technology Assessment

Clinical Specialty

Cardiology

Emergency Medicine

Geriatrics

Internal Medicine

Pathology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Hospitals

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical and cost-effectiveness of the Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I, and the

AccuTnI+3 assays for early rule out or diagnosis of acute myocardial infarction (without ST-segment elevation)

Target Population

People presenting with acute chest pain and suspected, but not confirmed, non-ST-segment elevation myocardial infarction (NSTEMI)

Interventions and Practices Considered

High-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I, and AccuTnI+3 assays) for early rule out of acute non-ST-segment-elevation myocardial infarction (NSTEMI)

Major Outcomes Considered

- Diagnostic and prognostic accuracy of high-sensitivity troponin tests, including sensitivity, specificity, positive and negative likelihood ratio (the numbers of true positive, false negative, false positive and true negative test results)
- Early discharge (≤4 hrs after initial presentation) without major adverse cardiac events (MACE) during follow-up, incidence of MACE during follow-up, re-attendance at or re-admission to hospital during follow-up, time to discharge, patient satisfaction or health-related quality of life (HRQoL) measures
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Systematic Review Methods

Search Strategy

Search strategies were based on intervention (high-sensitivity troponin [Tn] assays) and target condition, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.

Candidate search terms were identified from target references, browsing database thesauri (e.g., Medline MeSH and EMBASE Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches were used to generate test sets of target references, which informed text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity.

The following databases were searched for relevant studies from 2005 to October 2013:

- MEDLINE (OvidSP): 2005-2013/10/wk1
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 2013/10/1
- EMBASE (OvidSP): 2005-2013/10/10
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Cochrane Library Issue 10 2005-2013/10/11
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Cochrane Library Issue 9 2005-2013/10/11
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): Cochrane Library Issue 3 2005-July 2013
- Health Technology Assessment Database (HTA) (Wiley): Cochrane Library Issue 3 2005-July 2013
- Science Citation Index (SCI) (Web of Science): 2005-2013/10/14
- Conference Proceedings Citation Index – Science (CPCI) (Web of Science): 2005-2013/10/14
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet): 2005-2013/10/11 http://regional.bvsalud.org/php/index.php?lang=en
- International Network of Agencies for Health Technology Assessment (INAHTA) Publications (Internet): 2005-2013/10/15 http://www.inahta.org/
- Biosis Previews (Web of Knowledge): 2005-2013/10/11
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (Internet): 2005-2013/10/14
- Aggressive Research Intelligence Facility (ARIF) database (Internet): 2005-2013/10/16 http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx
- MEDION database (Internet): 2005-2013/10/16 http://www.mediondatabase.nl/
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet): up to 2013/10/10 http://www.crd.york.ac.uk/prospero/

Completed and on-going trials were identified by searches of the following resources (2005-present):

- National Institute of Health (NIH) ClinicalTrials.gov (Internet): up to 2013/10/1 http://www.clinicaltrials.gov/
- Current Controlled Trials (Internet): up to 2013/10/10
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2013/10/10 http://www.who.int/ictrp/en

No restrictions on language or publication status were applied. Date restrictions were applied based on expert advice on the earliest appearance of literature of high sensitivity Tn assays. Searches took into account generic and other product names for the intervention. The main EMBASE strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the Canadian Agency for Drugs and Technologies in Health (CADTH) Peer Review Checklist. Search strategies were developed specifically for each database and the keywords associated with high sensitivity troponin T or I (TnT/I) were adapted according to the configuration of each database. Full search strategies are reported in Appendix 1 in the DAR.

Electronic searches were undertaken for the following conference abstracts (selected based on advice from expert committee members):

- American Heart Association (AHA) Scientific Sessions (Internet): 2009-2013 http://my.americanheart.org/professional/Sessions/ScientificSessions/Archive/Archive-Scientific-Sessions_UCM_316935_SubHomePage.jsp
- American Association for Clinical Chemistry (AACC) (Internet): 2009-2013 http://www.aacc.org/
- European Society of Cardiology (ESC) (Internet): 2009-2013 http://spo.escardio.org/abstract-book/search.aspx

Identified references were downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles were checked for additional studies. The final list of included papers were checked on PubMed for retractions, errata and related citations.

Inclusion and Exclusion Criteria

Inclusion criteria for each of the clinical effectiveness questions are summarised in Table 2 in the DAR. Studies which fulfilled these criteria were eligible for inclusion in the review.

Inclusion Screening

Two reviewers independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed

these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in Appendix 4 in the DAR.

Studies cited in materials provided by the manufacturers of high sensitivity cardiac troponin (hs-cTn) assays were first checked against the project reference database, in Endnote X4; any studies not already identified by our searches were screened for inclusion following the process described above.

Assessment of Cost-effectiveness

Review of Economic Analyses of hs-cTn Assays

Search Strategy

Searches were undertaken to identify cost-effectiveness studies of high sensitivity TnT/I. As with the clinical effectiveness searching, the main EMBASE strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the CADTH Peer Review Checklist. Search strategies were developed specifically for each database and keywords associated with high sensitivity TnT/I were adapted according to the configuration of each database. Full search strategies are reported in Appendix 1 in the DAR.

The following databases were searched for relevant studies from 2005 to October 2013:

- MEDLINE (OvidSP): 2005-2013/10/wk1
- MEDLINE In-Process Citations and Daily Update (OvidSP): up to 2013/10/1
- EMBASE (OvidSP): 2005-2013/10/17
- National Health Service Economic Evaluation Database (NHS EED) (Wiley): Cochrane Library Issue 3 2005-July 2013
- Health Economic Evaluation Database (HEED) (Wiley): 2005-2013/10/18
- EconLit (EBSCO): 2005-2013/09/01
- Science Citation Index (SCI) (Web of Science): 2005-2013/10/21
- Conference Proceedings Citation Index – Science (CPCI) (Web of Science): 2005-2013/10/21
- Research Papers in Economics (REPEC) (Internet): up to 2013/10/21 http://repec.org/

Identified references were downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles were checked for additional studies.

Inclusion Criteria

Studies reporting a full economic analysis, which related explicitly to the cost-effectiveness of hs-cTn or standard cTn (with cTn implying either cTnI or cTnT) testing, with survival and/or quality-adjusted life years (QALYs) as an outcome measure, were eligible for inclusion. Specifically, one of the strategies had to include cTn testing. Studies that only reported a cost-analysis of cTn testing were not included in the review.

Number of Source Documents

Assessment of Clinical Effectiveness

The literature searches of bibliographic databases identified 6,766 references. After initial screening of titles and abstracts, 261 were considered to be potentially relevant and ordered for full paper screening; of these 35 were included in the review. All potentially relevant studies cited in documents supplied by the test manufacturers had already been identified by bibliographic database searches. One additional study was identified from hand searching of conference abstracts, and two additional studies were identified from information supplied by clinical experts. Therefore, 38 publications of 18 studies were included in the review. Figure 1 in the Diagnostics Assessment Report (DAR) (see the "Availability of Companion Documents" field) shows the flow of studies through the review process, and Appendix 4 in the DAR provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage.

Assessment of Cost-effectiveness

- The literature search identified 152 reports. After initial screening of titles and abstracts, five reports were considered potentially relevant: two full papers, and three Health Technology Assessment (HTA) reports. Two additional reports were identified provided by a clinical expert: a Canadian optimal use report (comparable to an HTA report) and an abstract which was referred to in this report. All seven identified reports fulfilled inclusion criteria based on full text assessment. The seven publications related to five studies. Figure 13 shows the flow of studies through the review process, Table 9 lists the study details, and the results of the quality assessment are shown in Table 10 in

the DAR (see the "Availability of Companion Documents" field).
- The Assessment Group also submitted an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an External Assessment Group to perform a systematic literature review on the technology considered in this diagnostics guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this guidance was prepared by the Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University (see the "Availability of Companion Documents" field).

Assessment of Clinical Effectiveness

Systematic Review Methods

Data Extraction

Data were extracted on the following: study details, inclusion and exclusion criteria, participant characteristics (demographic characteristics and cardiac risk factors), target condition (non-ST segment elevation myocardial infarction [NSTEMI] or acute myocardial infarction [AMI]), details of the high sensitivity cardiac troponin T [hs-cTnT] or high sensitivity cardiac troponin I (hs-cTnI) test (manufacturer, timing, and definition of positive diagnostic threshold), details of reference standard (manufacturer, timing, diagnostic threshold for conventional Tn T or I testing, clinical and imaging components of the reference standard, method of adjudication (e.g., two independent clinicians), and test performance outcome measures (numbers of true positive, false positive, false negative, and true negative test results). Data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second; any disagreements were resolved by consensus. Full data extraction tables are provided in Appendix 2 in the DAR.

Quality Assessment

The methodological quality of included diagnostic test accuracy (DTA) studies was assessed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). Quality assessments was undertaken by one reviewer and checked by a second; any disagreements were resolved by consensus. The results of the quality assessments are summarised and presented in tables and graphs in Section 3.2 and are presented in full, by study, in Appendix 3 in the DAR.

Methods of Analysis/Synthesis

Sensitivity and specificity were calculated for each set of 2x2 data and plotted in receiver operating characteristic space. The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive hierarchical summary receiver operating characteristic curves for meta-analyses involving four or more studies. This approach allows for between-study heterogeneity in sensitivity and specificity, and for the trade-off (negative correlation) between sensitivity and specificity commonly seen in diagnostic meta-analyses. For meta-analyses with fewer than four studies the Assessment Group estimated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression.

Heterogeneity was assessed visually using summary receiver operating characteristic plots and statistically using the variance of logit (sensitivity) and logit (specificity), where "logit" indicates the logistic function: the smaller these values the less heterogeneity between studies. Summary positive and negative likelihood ratios were derived from the summary estimates of sensitivity and specificity. Analyses were performed in Stata 10 (StataCorp LP, College Station, Texas, USA), mainly using the metandi command. For analyses that would not run in Stata, MetaDisc was used.

Analyses were conducted separately for each of the three hs-cTn assays. Analyses were stratified according to whether the study evaluated the prediction of AMI or major adverse cardiac event (MACE), timing of collection of blood sample for testing, and the threshold used to define a positive hs-cTn result. The Assessment Group investigated possible sources of heterogeneity using stratified analyses based on the following variables:

- Population: studies included mixed populations compared to those that excluded patients with STEMI.
- Age >70 years compared to age ≤70 years
- Patients with pre-existing coronary artery disease (CAD) at baseline compared to patients without pre-existing CAD
- Time from symptom onset to presentation <3 hours compared to >3 hours
- Time from symptom onset to presentation <6 hours compared to >6 hours
- Low to moderate pre-test probability of disease compared to high pre-test probability of disease

Stratified analyses were conducted for all time points and thresholds for which sufficient data were available. To investigate the influence of risk of bias on the studies the Assessment Group restricted analyses to studies conducted in patients at low or unclear risk of bias for the two QUADAS items considered to have the greatest potential to have introduced bias into these studies: the item on patient spectrum (1) and the item on patient flow (4). As the focus of this review was the diagnosis of NSTEMI, these analyses were conducted in studies that excluded patients with ST-segment elevation myocardial infarction (STEMI). The Assessment Group used summary receiver operating characteristic (ROC) plots to display summary estimates from the various primary and stratified analyses.

The accuracy of the three different hs-cTn assays were compared by tabulating summary estimates from analyses for common time points and thresholds assessed for all assays. Only one study provided a direct comparison of all three assays. Estimates of sensitivity, specificity, and positive and negative likelihood ratio (LR+ and LR-) for each assay derived from this study were included in the summary tables.

See Section 3.2 in the DAR for more information on the clinical effectiveness assessment.

Assessment of Cost-effectiveness

Review of Economic Analyses of hs-cTn Assays

Quality Assessment of Existing Studies

Full cost-effectiveness studies were appraised using the Drummond checklist.

Model Structure and Methodology

Troponin Tests Considered in the Model

Two hs-cTn assays (Elecsys hs-cTnT and ARCHITECT hs-cTnI) are currently used in National Health Service (NHS) laboratories in England and Wales. One additional assay (hs-cTnI) was listed in the scope for this assessment, pending CE marking. However, each of these tests can be used at different time points and with different diagnostic thresholds, resulting in multiple possible strategies for each test. Whether or not a test strategy was included in the economic model was decided based on optimal diagnostic performance given the available evidence on accuracy for a population with STEMI ruled out, and on applicability in clinical practice (see Section 3.2 of the DAR). The test strategies evaluated in the model are:

- Standard troponin at presentation and at 10 to 12 hours (reference standard)
- Elecsys hs-cTnT at presentation: 99th centile threshold
- Elecsys hs-cTnT (optimal strategy): limit of blank (LoB) threshold at presentation followed by 99th centile threshold peak within three hours and/or Δ20% (compared to presentation test) at 1 to 3 hours
- ARCHITECT hs-cTnI at presentation: 99th centile threshold
- ARCHITECT hs-cTnI (optimal strategy): limit of detection (LoD) threshold at presentation, followed by 99th centile threshold at three hours
- hs-cTnI (AccuTnI+3) at presentation: 99th centile threshold
- No testing, discharge all patients without testing or treatment (only in sensitivity analyses). A troponin test may not be indicated when clinical judgment assesses the probability that a patient is experiencing an AMI as low. Therefore, consistent with the protocol, this hypothetical

strategy is included in sensitivity analyses wherein the AMI prevalence is varied.

Based on the available evidence, two analyses were performed:

- Base case analysis
- Secondary analysis, assuming that false positives in the hs-cTn testing strategies do not have the same risk for adverse events as true negatives. Instead, these patients were assigned a higher risk for (re-)infarction and death, to reflect the idea that when the hs-cTn test gives a positive result, in some cases this must be caused by a disease process, whether or not the strict definition of AMI is met. The risk of adverse events in patients with positive hs-cTn but a negative standard troponin is higher than the patients testing negative on both the hs-cTn test and the standard troponin, but lower than risk of adverse events in patients diagnosed with NSTEMI (i.e., both positive hs-cTn and standard troponin).

Model Structure

The Assessment Group received the health economic model (in Simul8; SIMUL8 Corporation) that this Health Technology Assessment (HTA) was based on, and this model was used as a starting point to develop a *de novo* model (in Microsoft Excel) adapted to better fit the scope of the current assessment. In the health economic model the mean expected costs and quality-adjusted life years (QALYs) were calculated for each alternative strategy. These long-term consequences were estimated based on the accuracy of the different testing strategies followed by AMI treatment or discharge from the hospital without AMI treatment for patients presenting at the emergency department with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS), including patients with NSTEMI and patients without NSTEMI, who are further subdivided into 'no ACS, no unstable angina (UA)' and 'UA'. For this purpose a decision tree and a Markov model were developed. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. These outcomes consisted of 'no ACS, no UA', 'UA', 'Non-fatal AMI (untreated)', 'Non-fatal AMI (treated)' and 'Death'. The decision tree is shown in Figure 14 in the DAR. The long-term consequences in terms of costs and QALYs were estimated using a Markov cohort model (see Figure 15 in the DAR) with a lifetime time horizon (60 years).

See Section 4 in the DAR additional information on cost-effectiveness assessment.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Developing Recommendations

After reviewing the evidence the Diagnostic Advisory Committee (DAC) agrees draft recommendations on the use of the technology in the National Health Service (NHS) in England. When formulating these recommendations, the Committee has discretion to consider those factors it believes are most appropriate to the evaluation. In doing so, the Committee has regard to any relevant provisions of the National Institute for Health and Care Excellence's (NICE's) Directions, set out by the Secretary of State for Health, and legislation on human rights, discrimination and equality. In undertaking evaluations of healthcare technologies, NICE takes into account the broad balance of clinical benefits and costs, the degree of clinical need of patients under consideration, any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of NICE by the Secretary of State, and any guidance issued by the Secretary of State, and the potential for long-term benefits to the NHS of innovation.

The Committee takes into account advice from NICE on the approach it should take to making scientific and social value judgements. Advice on social value judgements is informed in part by the work of NICE's Citizens Council.

The Committee takes into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: race, gender, disability, religion or belief, sexual orientation, gender reassignment and pregnancy or maternity.

The Committee considers the application of other Board-approved NICE methods policies, such as the supplementary guidance on discounting and the end-of-life criteria, if they are relevant to the evaluation.

Because the Programme often evaluates new technologies that have a thin evidence base, in formulating its recommendations the Committee balances the quality and quantity of evidence with the expected value of the technology to the NHS and the public.

The credibility of the guidance produced by NICE depends on the transparency of the DAC's decision-making process. It is crucial that the DAC's decisions are explained clearly, and that the contributions of registered stakeholders and the views of members of the public are considered. The reasoning behind the Committee's recommendations is explained, with reference to the factors that have been taken into account.

The language and style used in the documents produced by the Committee are governed by the following principles:

- Clarity is essential in explaining how the DAC has come to its conclusions.
- The text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This needs careful judgement so that enough information and justification is given in the recommendations to enable the reader to understand what evidence the DAC considered and, if appropriate, who provided that evidence.

The Committee may take into account factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the reference-case cost analysis, such as improved processes.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Systematic Review of Cost-effectiveness

The results of the studies included in the systematic review varied widely, and the External Assessment Group concluded that the review demonstrated uncertainty about the cost-effectiveness of diagnostic strategies incorporating high-sensitivity troponin testing. The External Assessment Group noted that the key drivers of cost-effectiveness in the included studies were the accuracy of high-sensitivity troponin assays, and the efficiency of decision-making once test results were available.

Economic Analysis

The External Assessment Group developed a *de novo* economic model designed to assess the cost-effectiveness of 5 high-sensitivity troponin test strategies using 3 high-sensitivity assays: the Elecsys Troponin T high-sensitive assay, the ARCHITECT STAT High Sensitive Troponin-I assay, and the AccuTnI+3 troponin I assay.

Base-Case Results

The base-case analysis included 6 test strategies: 5 high-sensitivity troponin test strategies and the comparator, standard troponin testing over 10–12 hours. The results of the base-case analysis suggested that standard troponin testing was the most effective (15.101 life years, 11.730 quality-adjusted life years [QALYs]) and most expensive (£2697) test strategy. In contrast, the ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation sample was the least effective (15.076 life years, 11.712 QALYs) and least expensive (£2,253). The incremental cost-effectiveness ratios (ICERs) for the high-sensitivity troponin test strategies ranged from £24,019 to £90,725 saved per QALY lost compared with standard troponin.

Base-Case Subgroup Analyses

The External Assessment Group performed the following subgroup analyses: sex (stratified by age), history of previous ST-segment elevation myocardial infarction (STEMI), and acute myocardial infarction (AMI) prevalence based on clinically relevant subgroups defined in the scope. With the exception of AMI prevalence, the subgroups were defined on the basis that these characteristics may be associated with physiological differences in peak troponin levels.

For women, the ICERs increase with age, and by age 75 years, ICERs for all the high-sensitivity troponin testing strategies compared with standard troponin testing were over £30,000 saved per QALY lost, with the ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation test strategy having the lowest ICER (£32,776). The same effect of age was seen for men. However, by age 55 years, ICERs for all the high-sensitivity troponin testing strategies compared with standard troponin testing were over £30,000 saved per QALY lost, with the ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation test strategy having the lowest ICER (£30,338).

The External Assessment Group also conducted a subgroup analysis of AMI prevalence which suggested that when AMI prevalence is 1%

(compared with 17% in the base-case analysis), the no-testing strategy had an ICER of £96,456 saved per QALY lost. These subgroup analyses were performed with non-subgroup-specific accuracy data, and on this basis it is likely that there is substantial uncertainty surrounding the cost-effectiveness of the high-sensitivity troponin testing strategies in the reported subgroups.

Subgroup analyses were also undertaken based on test accuracy and AMI prevalence derived from the External Assessment Group's clinical effectiveness review. The following subgroups were considered in these analyses: aged 70 years or under and aged over 70 years, people with and without pre-existing coronary artery disease and symptom onset less than 3 hours before presentation or more than 3 hours before presentation. These analyses could only be performed for the Elecsys Troponin T high-sensitive 99th percentile presentation strategy because of the availability of subgroup data in the clinical-effectiveness review. In all subgroups the Elecsys Troponin T high-sensitive assay was less costly and less effective than standard troponin testing, but greater cost savings were reported for people aged younger than 70 years, people with pre-existing coronary artery disease, and people presenting within 3 hours of symptom onset. The limited availability of subgroup specific accuracy data means that it is likely that there is substantial uncertainty surrounding the cost-effectiveness of the high-sensitivity troponin testing strategies in the reported subgroups.

See Sections 5 and 6 in the original guideline document for additional information on cost-effectiveness.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The National Institute for Health and Care Excellence (NICE) sends the Diagnostics Assessment Report (DAR), with any confidential material removed, to registered stakeholders for comment. Stakeholders have 10 working days to return comments. Models supporting the DAR are made available to registered stakeholders on request during this period.

NICE presents anonymised registered stakeholder comments on the DAR, along with any responses from NICE or the External Assessment Group (EAG), to the Committee and later publishes these comments on its website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Diagnostics Advisory Committee considered clinical and cost-effectiveness evidence from a systematic review of high-sensitivity troponin assays performed by an external review group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Using high-sensitivity troponin assays (Elecsys Troponin T high-sensitive and ARCHITECT STAT High Sensitive Troponin-I) enables earlier detection of changes in troponin levels. This allows non-ST-segment elevation myocardial infarction (NSTEMI) to be ruled out within 4 hours, if test results are available within 3 hours of presentation to the emergency department. The increased sensitivity of these assays could mean a shorter inpatient hospital stay for people without raised levels of troponin and earlier intervention for those with a confirmed NSTEMI.

Potential Harms

False-positive or false-negative results. However, the Advisory Committee concluded that, in routine practice, clinical judgement is likely to reduce

the impact of both false-positive and false-negative results.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The National Institute for Health and Clinical Excellence (NICE) has developed tools (see also the "Availability of Companion Documents" field), in association with relevant stakeholders, to help organisations put this guidance into practice.
- Laboratories using high-sensitivity troponin assays should be able to show compliance with an accredited external quality assurance scheme. The use of the early rule-out protocols (see the "Major Recommendations" field) are conditional on laboratories meeting agreed turnaround times for high-sensitivity troponin tests and clinicians being available so that a management decision can be made within the 4-hour target for emergency departments.

Implementation Tools

Audit Criteria/Indicators

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 53 p. (Diagnostics guidance; no. 15).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Oct

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

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National Institute for Health and Care Excellence (NICE)

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Diagnostics Advisory Committee

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Financial Disclosures/Conflicts of Interest

Committee members are required to submit a declaration of interests on appointment, in every year of their tenure, and at each Committee meeting, in line with the National Institute for Health and Care Excellence's (NICE's) code of practice for declaring and dealing with conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Westwood ME, van Asselt ADI, Ramaekers BLT, Whiting P, Thokala P, Joore MA, Armstrong N, Ross J, Severens JL, Kleijnen J. High sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis. Diagnostics assessment report. York (UK): Kleijnen Systematic Reviews Ltd; 2014. 250 p. Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 5 p. (Diagnostics guidance; no. 15). Available from the NICE Web site .
- Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). Clinical audit tool. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. (Diagnostics guidance; no. 15). Available from the NICE Web site .
- Myocardial infarction (acute): Early rule out using highâ€‘sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). Diagnostic adoption support. London (UK): National Institute for Health and Care Excellence (NICE). 2014 Oct. Available from the NICE Web site .
- Diagnostics Assessment Programme manual. London (UK): National Institute for Health and Care Excellence; 2011 Dec. 130 p. Available from the NICE Web site .

Patient Resources

The following is available:

- Myocardial infarction (acute): early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). Information for the public. London (UK): National Institute for Health and Care

Excellence (NICE); 2014 Oct. (Diagnostics guidance; no. 15). Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on January 2, 2015.

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